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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,163	12/20/2001	Sanjay Lakhotia	AM100039	1674
25291	7590	04/10/2006	EXAMINER	
WYETH PATENT LAW GROUP 5 GIRALDA FARMS MADISON, NJ 07940			FORD, VANESSA L	
			ART UNIT	PAPER NUMBER
			1645	

DATE MAILED: 04/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,163	LAKHOTIA ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 9/8/05.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-16 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 12/20/2001 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/25/03</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed December 1, 2005.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Maintained

3. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-16 for the reasons set forth on pages 3-5 paragraph 4 of the previous Office Action.

The rejection was on the grounds that Van Reis et al teach a method of industrial scale harvest of mammalian proteins by tangential flow filtration (TFF). Van Reis teach that methods such as conventional centrifugation, liquid-liquid extraction, rotary filtration offer high shear environments, slow recovery processes, high cost and the use of dead -end cartridges (pages 413-414). Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work (page 421).

Van Reis et al do not teach extracting native or recombinant inner and outer membrane proteins from bacteria.

Green et al teach a method of purifying bacteria using detergents such as Triton™ (column 4). Green et al teach that in a preferred embodiment the outer membrane components are prepared by differential solubilization of the inner membranes using Triton™ in HEPES-NaOH and MgCl₂. Green et al teach that a subfraction of the preparation of the outer membrane components which is rich in protein "e" (outer membrane protein P4 from *Haemophilus influenzae*) can be produced by extraction with an aqueous solution (column 4). Green et al teach that the protein "e" from the outer membrane cell wall complex can be then achieved by a two-step differential solubilization with sulfobetaine detergents (column 4). Green et al teach that the first step comprises an aqueous solution of Zwittergent™ to remove other outer membrane proteins other than protein "e" (column 4). Green et al teach that the residual insoluble components are then extracted with an aqueous solution of Zwittergent™ and this fraction results in the solubilization of protein "e" (column 4). Green et al teach that this process is performed in a homogenizer (column 14) since the instant specification teaches that a homogenizer is a microfluidizer (page 10 of the specification). Green et

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al teach that recombinant protein "e" can be isolated and purified by differential solubility (column 9).

It would be *prima facie* obvious at the time the invention was made to use tangential flow filtration as taught by van Reis et al to extract bacterial proteins (inner and outer membrane) because Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work. It would be expected barring evidence to the contrary that using tangential flow filtration in a method of extracting proteins would offer high quality and high yield proteins at a low cost.

Applicant urges that van Reis article is a simplistic restatement that tangential flow filtration (TFF) systems can be used to separate materials according to molecular weight. Applicant urges that Green et al disclose a method of purifying P4 by differential detergent extraction utilizing physical processing methods, none of which rely on molecular size differences. Applicant urges that none of the proteins extracted by the processes of the prior art are required to pass through a diafiltration membrane. Applicant urges that motivation, suggestion or teaching may be found in explicit or implicit teachings within the references themselves from ordinary knowledge of those skilled in the art or from nature of the problem to be solved. Applicant urges that there is no suggestion to combine the prior art references to arrive at the claimed invention.

Examiner's Response to Applicant's Amendments

Applicant arguments filed December 1, 2005 have been fully considered but they are not persuasive.

It is the Examiner's position that Applicant is arguing the references individually. It should be remembered that it is the combination of references that teaches the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the skilled artisan would be motivated to used tangential flow filtration as taught by van Reis in the method of extracting proteins of Green et al because van Reis et al teach that TFF has the a) benefit of low shear processing, b) complete cell containment, c) high yields, d) potential for linear upscale, e) low operating costs and f) the ability to use the same process from large number of products without additional development work.

The Examiner disagrees with Applicant's assertion that "none of the proteins extracted by the processes of the prior art are required to pass through a diafiltration membrane. It should be noted that Green et al teach that fractions containing protein

are pooled and concentrated by diafiltration or process that rely on molecular size differences. See column 14.

To address Applicant's comments regarding physical processing methods, it should be noted that Green et al uses physical as well as chemical extraction methods in the methods of the invention. For, example Green et al uses detergents as wells as aqueous solvents in the methods of the invention. See column 4. Applicant is reminded that the claims recite the transitional or open claim language "comprising" which can include other methods steps or reagents other than the steps or reagents that are contained in the claimed method. One skilled in the art would have a reasonable expectation of success by combining the prior art references to arrive at the claimed invention. There is nothing on the record to suggest that the combination of reference does not teach the claimed invention.

4. The rejection under 35 U.S.C. 103(a) is maintained for claims 1-16 for the reasons set forth on pages 5-7 paragraph 5 of the previous Office Action.

The rejection was on the grounds that Van Reis et al teach a method of industrial scale harvest of proteins by tangential flow filtration (TFF). Van Reis teach that methods such as conventional centrifugation, liquid-liquid extraction, rotary filtration offer high shear environments, slow recovery processes, high cost and the use of dead-end cartridges (pages 413-414). Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work (page 421).

Van Reis et al do not teach extracting native or recombinant inner and outer membrane proteins from bacteria.

Anilionis et al teach a method isolating and purifying of native and recombinant inner and outer membrane proteins from *Haemophilus influenzae* (columns 26-27). Anilionis et al teach that *Haemophilus influenzae* incubated in medium and centrifuged to form a cell pellet (columns 26-27). Anilionis et al teach that the cell pellet was

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suspended in HEPES-NaOH, EDTA and placed in a cell disruptor (columns 26-27). Anilionis et al teach that the total membrane fraction was separated into inner and outer membrane components by extraction with sarcosyl in HEPES-NaOH (column 27).

Van Reis et al and Anilionis et al do not teach divalent cations such as calcium to stabilize the outer membrane proteins.

Kolbe teaches that divalent metal ions such as calcium can form complexes with proteinaceous compounds (column 1). Kolbe teaches that divalent metal ions are commonly used in processes of purifying proteins either as coupling agents for affinity chromatography or to precipitate proteins from liquid medium (column 1).

It would be *prima facie* obvious at the time the invention was made to add the divalent metal ions as taught by Kolbe to the process of extracting proteins by tangential flow filtration as taught by van Reis et al and Anilionis et al combined because divalent metal ions such as calcium can form complexes with proteinaceous compounds and divalent metal ions are commonly used in processes of purifying proteins. It would be expected barring evidence to the contrary, that using tangential flow filtration as in a process for extracting inner and out membrane proteins both native and recombinantly made because Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work.

Applicants Arguments

Applicant urges that van Reis article is a simplistic restatement that tangential flow filtration (TFF) systems can be used to separate materials according to molecular weight. Applicant urges that Anillionis et al disclose a method of isolating and purifying outer membrane proteins P4 and P6 by differential detergent extraction utilizing sonication and centrifugation neither of the process rely on molecular size differences.

Applicant urges that these proteins are not required to pass through a diafiltration membrane. Applicant urges that Kolbe only relates to the claimed invention in that proteins are being purified. Applicant urges that motivation, suggestion or teaching may be found in explicit or implicit teachings within the references themselves from ordinary knowledge of those skilled in the art or from nature of the problem to be solved.

Applicant urges that there is no suggestion to combine the prior art references to arrive at the claimed invention.

Examiner's Response to Applicant's Amendments

Applicant arguments filed December 1, 2005 have been fully considered but they are not persuasive.

It is the Examiner's position that Applicant is arguing the references individually. It should be remembered that it is the combination of references that teaches the claimed invention.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the skilled artisan would be motivated to used tangential flow filtration as taught by van Reis in the method of extracting proteins of Anilionis et al because van Reis et al teach that TFF has the a) benefit of low shear processing, b) complete cell containment, c) high yields, d) potential for linear upscale, e) low operating costs and f) the ability to use the same process from large number of products without additional development work. It should be noted the Kolbe reference is added to teach the claim limitation "divalent metal ions".

The Examiner disagrees with Applicant's assertion that "none of the proteins extracted by the processes of the prior art are required to pass through a diafiltration membrane. It should be noted that Green et al teach that proteins can be obtained in the method of the invention by using a molecular sieve. A molecular sieve has pore ranges of a particular size that would exclude or include certain molecular weights. See column 14. Therefore one skilled in the art would reasonable conclude that Green et al teach as a part of their extraction process, method steps that include diafiltration or processes that rely on molecular size differences. One skilled in the art would have a reasonable expectation of success by combining the prior art references to arrive at the claimed invention. There is nothing on the record to suggest that the combination of reference does not teach the claimed invention.

Status of Claims

5. No claims allowed.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (571) 273-8300.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


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April 3, 2006


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